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METABOLOMICS AS PART OF AN INTEGRATED APPROACH FOR THE IDENTIFICATION OF PREDICTIVE MARKERS OF TYPE 2 DIABETES

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The trajectory and underlying mechanisms of human health are determined by a complex interplay between intrinsic and extrinsic factors. Its evolution is a continuum of transitions, involving multifaceted processes at multiple levels and there is an urgent need for integrative biomarkers that can characterize and predict health status evolution. The objective of the present study was to identify accurate and robust multidimensional markers, predictive of type 2 diabetes (T2D). A case-control approach was used within the French population-based cohort GAZEL (n~20,000) [1]. Male overweight subjects (n=112, 25≤BMI<30 kg/m², 52-64 y.o.), free of T2D at baseline, were selected. Cases were defined as having developed T2D at follow-up (5 years later) and were compared for several parameters (clinical, biochemical parameters, and food habits) with Controls matched for BMI, age, and sex. Baseline serum samples were analyzed using mass spectrometry-based untargeted metabolomics [2]. Data mining methods were used to select the best candidate for prediction. Models were built using linear logistic regressions on the resulting reduced dataset and their performances were determined by calculating the area under the receiver operating characteristics curve (AUC), along with their 95% confidence intervals (CI), as well as sensitivity and specificity values. Metabolomic data were integrated with the different parameters from the database in order to determine whether multidimensional models improve prediction. Associations between food habits, clinical parameters and serum metabolites were investigated using correlation networks. Clinical data showed significant differences between Cases and Controls regarding several parameters: body mass index (p=0.046), waist/hip ratio (p=0.005), blood pressures (p=0.005), fasting blood glucose level (p=5E-9), and consumption frequencies of vegetables (p=0.016) and sugar (p=0.0003). Thanks to its broad phenotyping power, the untargeted metabolomics approach allowed the identification of 5 predictive biomarkers. The resulting metabolite-only model showed better performances than the one built with clinical data: a lower misclassification rate (18% *vs* 26%) and a higher AUC (0.82 vs 0.74; CI: [0.748-0.892] *vs* [0.659-0.823]). Integration of metabolomic data with the available clinical and biochemical parameters allowed optimizing the prediction performances (10.8% misclassification, AUC=0.89, CI: [0.833-0.950]). Correlation network analyses contributed to explore the links between metabolic, clinical parameters, and food habits. Therefore, metabolomic markers when combined with clinical characteristics appeared to offer the possibility of better prediction of disease development. These results show the interest of an integrated approach including untargeted metabolomics in the discovery of predictive biomarkers 5 years before T2D occurrence. They should provide new tools to better stratify at-risk populations, as well as additional knowledge on T2D understanding. Project funded by the INRA DID'IT Metaprogramme.

KEYWORDS: metabolomics, biomarkers, prediction, type 2 diabetes, cohort

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